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Nonparametric Version of Williams' Test for a Randomized Block Design

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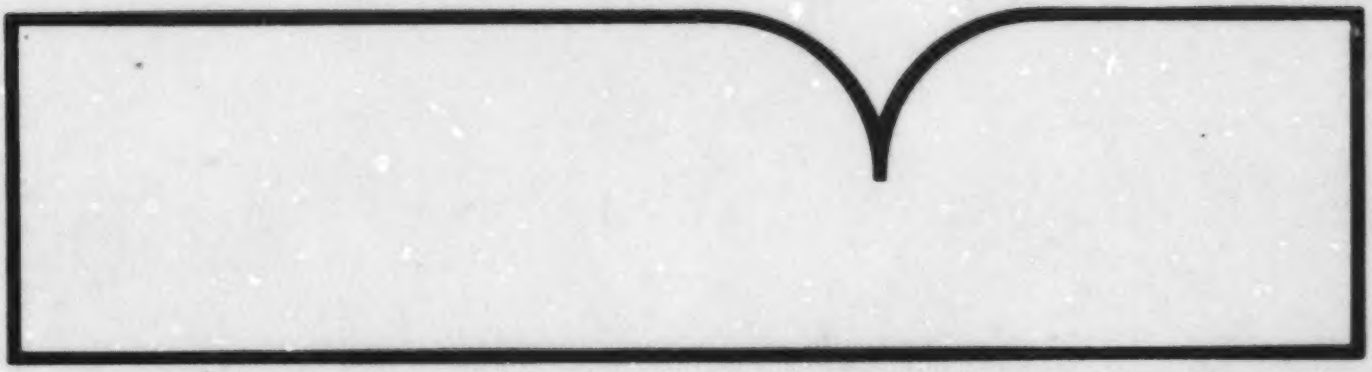

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A Nonparametric Version of Williams' Test for a Randomized Block Design

Dennis E. House

Biometry Division, MD-55, Health Effects Research Laboratory,
U.S. Environmental Protection Agency,
Research Triangle Park, North Carolina 27711, U.S.A.

SUMMARY

A large-sample nonparametric version of Williams' test for comparing increasing doses of a substance with a zero-dose control response is given for observations from a randomized block experimental design. The method is based on Friedman-type ranks. Williams' test and the nonparametric equivalent for a one-way design are briefly described. The validity of the new method is shown and a numerical example is given.

1. Introduction

The toxicity or other effects of substances such as drugs, pesticides, and various environmental pollutants can be assessed by either *in vitro* or *in vivo* studies. Increasing doses of the substance including a control or zero dose are usually employed in these experiments. In a completely randomized design, each dose is given to a different group of animals, cells, etc. The investigator wants to know if there is evidence of toxicity or other effects and, if so, at what dose levels. Williams (1971, 1972) gives a test for answering both questions. Shirley (1977) gives a large-sample Wilcoxon-type nonparametric equivalent of Williams' test. Williams (1986) gives a modification that increases the power of Shirley's test.

In some instances, such as when effects are short-term and reversible, it is possible to design a more powerful experiment by giving, for example, all doses in a randomized order to each animal and thereby introduce a blocking factor into the design. With a blocking factor present, Williams' test can still be used if the assumptions of the test are satisfied. But, if those assumptions are not satisfied, Shirley's nonparametric test cannot be used since it is inappropriate for the randomized block design. The purpose of this paper is to give a nonparametric version of Williams' test which is appropriate for a randomized block design.

2. Williams' Test

Williams' test assumes that the mean response of the variate is a monotonic function of dose. Suppose that k dose levels are compared with a control group and an upward trend in the means is suspected. The maximum likelihood estimates of the means, M_i, $i = 1, \ldots, k$, for each dose group are found under the constraint $M_1 \leq M_2 \leq \cdots \leq M_k$ by the formula

$$\hat{M}_i = \max_{1 \leq u \leq i} \min_{i \leq v \leq k} \sum_{j=u}^{v} r_j X_j \Big/ \sum_{j=u}^{v} r_j,$$

where X_i and r_i are the sample mean and sample size, respectively, for dose group i.

Key words: Friedman multiple comparisons; Nonparametric test; Williams' test.

The estimated residual variance, S^2, is obtained in the usual way and the statistic $\bar{t}_k = (\hat{M}_k - X_0)(S^2/r_k + S^2/c)^{-1/2}$ is calculated, where X_0 and c are the control group sample mean and sample size, respectively. One-sided and approximate two-sided critical values of $\bar{t}_k$ for both equal and unequal group replications are obtained from tables provided by Williams (1972).

The statistic $\bar{t}_k$ is tested first and if it is significant then $\bar{t}_{k-1}$ is calculated in the same way and compared to its critical value given in the tables. This process continues until a nonsignificant $\bar{t}_i$ is obtained for some dose i. The conclusion is that there is a significant effect for dose levels $i + 1$ and above and no significant evidence of a dose effect for levels i and below.

Under the null hypothesis that the means, M_i, are all equal and have equal replication, the statistic $\bar{t}_k$ is distributed as $(Y_k - Z_0)/S$ where Y_k, Z_0, and S are independent random variables,

$$Y_k = \max_{1 \le u \le k} \sum_{j=u}^{k} Z_j/(k - u + 1),$$

the Z_i are normally distributed with zero mean and unit variance, and $\frac{1}{2}pS^2$ has a chi-square distribution with p degrees of freedom. So Williams' test is appropriate for data that are normally distributed and have equal group variances. Williams calculated the distribution function of Y_k for each k, then calculated the distribution function of $\bar{t}_k$ and from this constructed the tables of critical values of $\bar{t}$.

Shirley (1977) gives a large-sample Wilcoxon-type nonparametric equivalent of Williams' test that is appropriate for a completely randomized design. The test involves ranking the combined data from the control and all dose groups and then computing the means of the ranks for all groups, $\bar{R}_0, \bar{R}_1, \ldots, \bar{R}_k$. Shirley shows that the distribution of

$$t_k = \left[\max_{1 \le u \le k}\left(\sum_{j=u}^{k} r_j\bar{R}_j \Big/ \sum_{j=u}^{k} r_j\right) - \bar{R}_0\right]\{[N(N+1)/12](1/r_k + 1/c)\}^{-1/2},$$

where $N = \sum_i r_i$, is approximately that of $\bar{t}_k$ with infinite degrees of freedom. If ties occur, average ranks are used and the variance correction factor given by Shirley should be applied.

3. Nonparametric Equivalent of Williams' Test for a Randomized Block Design

In each of n blocks, let there be an observation for each dose and the control, giving a total of $k + 1$ observations. The observations in each block are ranked, as in the Friedman (1937) two-way analysis of variance, and the vector of mean ranks $\bar{\mathbf{R}} = (\bar{R}_0, \bar{R}_1, \ldots, \bar{R}_k)$ is obtained. Miller (1966) showed that the k-fold vector of pair differences $(\bar{R}_1 - \bar{R}_0, \bar{R}_2 - \bar{R}_0, \ldots, \bar{R}_k - \bar{R}_0)$ follows an asymptotic normal distribution with the same correlation structure as that of $(Z_1 - Z_0, Z_2 - Z_0, \ldots, Z_k - Z_0)$ where the Z_i, $i = 0, \ldots, k$, are independent and normally distributed with zero mean and unit variance. So, in this instance, the equivalent of $Y_k - Z_0$ is

$$\max_{1 \le u \le k} \sum_{j=u}^{k} \bar{R}_j/(k - u + 1) - \bar{R}_0 = \max_{1 \le u \le k} \sum_{j=u}^{k} (\bar{R}_j - \bar{R}_0)/(k - u + 1).$$

Therefore, the distribution of

$$\left\{\max_{1 \le u \le k}\left[\sum_{j=u}^{k} \bar{R}_j/(k - u + 1)\right] - \bar{R}_0\right\}\{[(k+1)(k+2)/12](2/n)\}^{-1/2} \qquad (1)$$

is approximately that of $\bar{t}_k$ with infinite degrees of freedom.

If ties occur within a block, average ranks are used and the factor $(k + 1)(k + 2)/12$ is reduced by T where any group of t tied ranks contributes $(t^3 - t)/(12nk)$ to T.

Williams (1986) describes a modification to Shirley's test that results in a more powerful test for the sequential procedure. The argument used to justify this modification to Shirley's test applies also to the randomized block test, which should therefore be similarly modified. The modification consists of excluding all observations at the higher dose levels for which significance has been established, then reranking the remaining observations and applying equation (1) with k reduced by the number of higher doses excluded.

4. Example

As an example, consider the partially artificial data in Table 1 from an experiment designed to determine the lowest dose of sulfur dioxide (SO_2) with a significant increase in specific airway resistance (sRaw). Each subject (block) participated in four randomly ordered 10-minute exposures, one for each dose, which were separated by at least 1 week. The basic observation is the change in sRaw from pre-exposure to after 10 minutes of exposure. There is reason to believe that these data do not satisfy the assumptions of Williams' test nor are they appropriate for Shirley's test because of the randomized block design with the subject blocking factor. The rankings within subjects are given in the table next to the change.

To test for an effect at 1.0 ppm SO_2, the correction for ties is

$$5(2^3 - 2)/(12 \cdot 11 \cdot 3) = 0.0758$$

and

$$\bar{t}_3 = (3.25 - 1.64)\{[(4 \cdot 5/12) - 0.0758](2/11)\}^{-1/2} = 2.99.$$

For infinite degrees of freedom, the one-percent critical value for $\bar{t}_3$ is 2.377 (Williams, 1972). Hence, there is a significantly increased change in sRaw at 1.0 ppm SO_2.

Now, following the modification given by Williams (1986), we rerank the data for the three lowest doses. This gives mean ranks of 1.50, 1.68, and 2.82 for the 0.00, 0.25, and

Table 1
Changes[a] in sRaw (cm. H_2O/sec.) *and ranks for eleven subjects exposed to a control and three concentrations of* SO_2 (*ppm*)

	Concentration of SO_2 (ppm)							
	0.00		0.25		0.50		1.00	
Subject	Change	Rank	Change	Rank	Change	Rank	Change	Rank
1	0.2	2	2.3	3	−0.8	1	4.0	4
2	6.2	1	12.7	3	13.1	4	9.0	2
3	0.3	2	−0.2	1	1.1	3	4.2	4
4	0.3	1	2.1	2	12.8	4	6.7	3
5	4.9	1	6.0	2	18.2	3	35.0	4
6	1.8	1.5	1.8	1.5	3.4	3	9.0	4
7	3.9	1.5	3.9	1.5	13.5	4	12.9	3
8	2.0	2.5	1.1	1	4.4	4	2.0	2.5
9	0.3	1	3.8	2	6.1	3	7.1	4
10	2.5	2.5	2.5	2.5	2.8	4	1.5	1
11	5.4	2	1.3	1	10.6	3.5	10.6	3.5
Means		1.64		1.86		3.32		3.18

[a] 10-minute exposure measurement minus pre-exposure measurement.

0.50 ppm SO_2 doses, respectively. To test for an effect at 0.50 ppm SO_2, the correction for ties is

$$3(2^2 - 2)/(12 \cdot 11 \cdot 2) = 0.0682$$

and

$$\bar{t}_2 = (2.32 - 1.50)\{[(3 \cdot 4/12) - 0.0682](2/11)\}^{-1/2} = 3.21.$$

The one-percent critical value for $\bar{t}_2$ is 2.366, so there is a significantly increased change in sRaw at 0.50 ppm SO_2.

Reranking the two lowest doses gives mean ranks of 1.41 and 1.59 for the 0.00 and 0.25 ppm SO_2 doses, respectively. The correction for ties is

$$3(2^3 - 2)/(12 \cdot 11) = 0.1364$$

and

$$\bar{t}_1 = (1.59 - 1.41)\{[(2 \cdot 3/12) - 0.1364](2/11)\}^{-1/2} = 0.70,$$

which is well below the five-percent critical value of 1.645.

Résumé

On donne une version non paramétrique pour de grands échantillons du test de Williams ayant pour but de comparer l'effet de doses croissantes d'une substance à un témoin sur un plan d'expérience en blocs aléatisé. La méthode est fondée sur des rangs du type Friedman. On décrit brièvement le test de Williams et son équivalent non paramétrique sur le modèle à un facteur. On montre la validité de cette nouvelle méthode et on donne un exemple numérique.

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